



TITLE:

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Pathophysiology of the Liver of Hepatic Artery Ligated Dogs (Portal Dogs), with Special Reference to Their Tolerance to Shock

by

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Contents

| | |
|-------------------------------------|--|
| Introduction | a) Method |
| Experimental methods and results | b) Results |
| 1) Preparation of the portal dog | D Histological changes of liver |
| 2) Production of hemorrhagic shock | a) Method |
| 3) Wiggers-Werle's method | b) Results |
| a) Method | 5) Tolerance of portal dogs against portal |
| b) Results | vein ligation |
| 4) Lamson's method | a) Method |
| A Course of shock | b) Results |
| a) Method | Discussion |
| b) Results | Conclusion |
| B Development of irreversible shock | References |
| C Variation of hematocrit | |

INTRODUCTION

In 1905, HABERER¹⁾ reported a mortality rate of almost 100 % of animals subjected to complete interruption of hepatic arterial blood flow by ligation of this artery, which caused extensive liver necrosis. But in 1949, MARKOWITZ et al.²⁾³⁾ lowered this mortality rate from 100% to 35% by the administration of penicillin. HONJO⁴⁾ proved that the portal circulatory disturbance due to the interruption of hepatic artery was the major factor of the development of liver necrosis. Then, NAKASE⁵⁾ in our laboratory administered non-antibiotic drugs such as atropin or dibenamine for the purpose of mitigating the portal circulatory disturbance, and prevented the development of extensive liver necrosis which is fatal to animals, lowering the mortality rate to 30% which is similar to that of penicillin administered cases. Thus, when dogs survived for a long period after the interruption of hepatic arterial flow without showing any fatal liver necrosis, we called them "portal dogs", because the blood supply to the liver of those animals depends mainly on the portal vein.

On the other hand, there are many who attributed the cause of shock, especially that of irreversible shock, to the liver. The following two theories may be representative : One is V. D. M. theory by SHORR et al.⁶⁾⁷⁾⁸⁾⁹⁾ ; and the other is the bacterial toxin theory by FINE and his school¹⁰⁾¹¹⁾. The former insists that generalized hypotension

causes liver anoxia, then ferritin in the liver cells is mobilized and released into the blood stream as vasodepressor material (V. D. M.), breaking down the compensatory mechanism of the circulatory system. The latter assumes that continuous liver anoxia causes proliferation of anaerobic organisms in the liver and thus produced toxin, lecithinase, is the main agent in the development of irreversible shock.

Both of these theories agree in that liver anoxia plays an important role in the development of irreversible shock. As stated above, portal dogs are deprived of their arterial blood supply to the liver, so it may be questioned how the attitude of these dogs may be against shock which is in a close relationship to liver anoxia.

The author examined the effect of hemorrhagic shock and portal ligation in portal dogs, in order to study the pathophysiology of their liver, with special reference to their tolerance to shock.

EXPERIMENTAL METHODS AND RESULTS

1) Preparation of the portal dog

HUGGINS and POST¹²⁾ confirmed the fact that ligation of the hepatic artery and its largest collaterals, the gastroduodenal and right gastric, in one stage was always fatal in dogs. Besides these collaterals, there are small branches from the left gastric and phrenic arteries. However, URABE,¹³⁾ ISHIGURO¹⁴⁾ and others clarified the fact that the common hepatic, gastroduodenal and right gastric arteries (hereafter, these arteries will be called the three major hepatic arteries in the present report), which communicate with the hepatic hilum and supply the blood systematically to the whole liver, play a decisive role in the oxygen supply to the liver, while the other small arterial branches supply the blood only to the surface or a localized portion of the liver.

Mongrel, adult dogs weighing from 6 to 14 kg were used for preparation of the portal dog. General anesthesia with intravenous injection of pentobarbital sodium of 25 mg per kg of body weight was applied. Double ligation and severing of the three major hepatic arteries and simultaneous cholecystectomy were carried out through an upper midline incision. Intraperitoneal injection of aqueous penicillin of 100 000 U. was given before the closure of the abdominal cavity and intramuscular injection of penicillin in oil 300,000 U. was given immediately after the operation, and further twice every 24 hours. The mortality rate of this procedure was 34%.

There was no significant difference in the mortality rate when cholecystectomy was added to hepatic artery ligation, but about 50% of survivals developed localized bile peritonitis due to perforation of the gall bladder and they were markedly emaciated compared with those which did not develop perforation. Therefore, in the present experiment the cholecystectomy was performed in all cases of hepatic artery ligation.

According to FRASER¹⁵⁾, KURAMOTO¹⁶⁾ and MIYAZAKI¹⁷⁾, dogs survived for long after the ligation of three major hepatic arteries—portal dogs—usually recovered from postoperative impairment of liver function by the 10th postoperative day to nearly normal state. On the other hand, URABE¹³⁾ and ISHIGURO¹⁴⁾ made some research on the regeneration of the arteries, following the ligation of three major hepatic arteries, by roentgenological study or by synthetic resin cast preparation. From their results they found that no col-

lateral vessels large enough to compensate the ligated three major hepatic arteries have developed within two weeks after the operation.

Referring to these facts, obviously healthy portal dogs were used in the present experiment within two weeks after the operation.

2) Production of hemorrhagic shock

There are two methods of producing hemorrhagic shock in animals: one is WIGGERS-WERLE's method¹⁸⁾¹⁹⁾²⁰⁾, and the other is LAMSON's one²¹⁾. The former retains a certain grade of hypotension for a certain period by adequate withdrawal and transfusion of blood, and the latter obtains the desired hypotension by connecting an artery to an irrigator with a rubber tube to control the amount of bleeding by adjusting the height of its position. Usually animals are apt to reveal considerable individual difference in vital response. Accordingly, in the study of tolerance to hemorrhagic shock, WIGGERS-WERLE's method is not only inconvenient but inaccurate in obtaining a certain periodical pattern, since blood pressure is the only indicator.

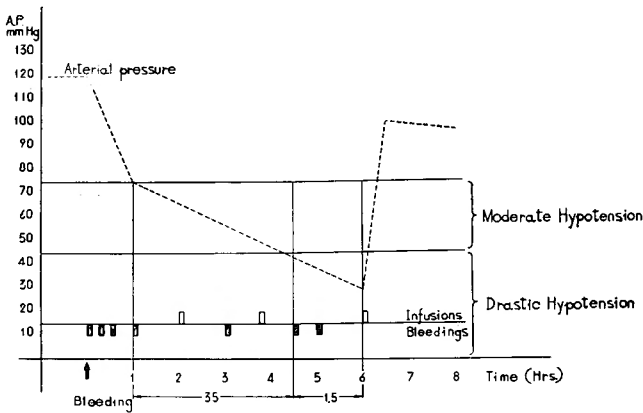
In LAMSON's method, arbitrary blood pressure is obtainable and regardless of manifold individuality of experimental animals, three stages are easily observed in sequence. At first, the bleeding stage appears when continuous bleeding into the bottle is seen, then the balanced stage follows when there is no change in blood volume in the bottle, and finally the stage of spontaneous return of blood comes in which the disturbance in compensatory mechanism of circulatory system develops and blood pressure decreases so that the blood in the bottle automatically returns to the circulatory system of animals. This method makes it convenient to discriminate the shock stages from each other. Both methods were applied in the present experiment in producing hemorrhagic shock, and responses of portal dogs were compared with those of normal ones.

3) WIGGERS-WERLE's method

Hemorrhagic shock by WIGGERS-WERLE's method was carried out on three normal and portal dogs, respectively.

a) Method: Mongrel, adult dogs weighing from 6.5kg to 12kg were used. Under general anesthesia with intravenous injection of pentobarbital sodium of 25 mg/kg of body weight, bilateral femoral arteries were exposed. Heparin of 5 mg/kg was injected intravenously to prevent blood coagulation. A needle of about 1 mm caliber was inserted into one of the femoral artery and connected to an electric sphygmomanometer with a vinyl tube to monitor arterial blood pressure. The other femoral artery was used for withdrawal and transfusion of blood. As for the method of producing hemorrhagic shock, the standard type by ZWEIFACH et al.²²⁾²³⁾ was followed. As shown in Fig. 1, 2.0, 1.0, 0.5 and 0.25% of the body weight of blood was respectively drawn out at intervals of 15 minutes. The arterial blood pressure was lowered to moderate hypotension which was between 75 and 50 mmHg and maintained within this range for 3 or 4 hours by appropriate control of drawing or transfusion of blood according to the blood pressure. Withdrawn blood was reserved in an irrigator. Succeedingly, arterial blood pressure was lowered to drastic hypotension, which is below 45 mmHg, by the same procedure and maintained in this condition for about 1.5 hours. Then the entire withdrawn blood was transfused through the artery. By this transfusion, arterial blood pressure was rapidly

Fig. 1. Changes of arterial pressure in typical pattern of hemorrhagic shock (WIGGERS-WERLE's method)



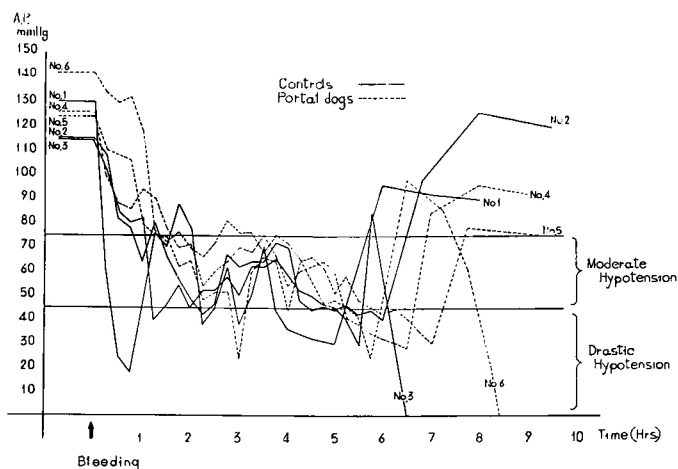
elevated and came close to the level maintained before the withdrawal. After that, the attitudes of experimental dogs differed from each other, depending upon the animal's condition at the time of the last transfusion. Animals which developed marked lowering of blood pressure within two hours and finally driven to death should be said to have been in a state of irreversible shock ; and those which maintained the normal blood pressure for over two hours to have been in a reversible shock. When unexplainable sudden death occurred or transfusion was impossible due to blood coagulation during the experiment, animals were excluded from the results.

b) Results : The results of the experiment are shown in Table 1 and Fig. 2. Comparing with the result of FINE et al.¹⁰⁾ in normal dogs, bleeding of 5.3% of body weight, 5.3 hours of hypotension and 76% of mortality rate and that of ZWEIFACH²¹⁾, bleeding of 4.0% of body weight, 4.5 to 6.0 hours of hypotension, and 82% of mortality rate, a smaller mortality rate was obtained in the present experiment. The duration of moderate hypotension in normal dogs was 3.5 hours in each three cases, and that of drastic hypotension was 1 to 1 hour and 45 minutes; one case developed irreversible shock. In the group of portal dogs, the duration of moderate hypotension was 3 hours and 20

Table 1 Hemorrhagic Shock by WIGGERS-WERLE's Method

| | No. | Body Weight kg | Arterial Pressure mmHg | Bleeding Volume | | Period of Moderate Hypotension | | Period of Drastic Hypotension | | Results |
|----------------|------|-------------------|------------------------------|-----------------|--------------------------|--------------------------------------|-------|-------------------------------------|-------|----------|
| | | | | Volume cc | Ratio to Body Wt. (%) | Hrs. | Mins. | Hrs. | Mins. | |
| Controls | 1 | 8.0 | 130 | 380 | 4.8 | 3.30 | | 1.15 | | survived |
| | 2 | 10.5 | 114 | 558 | 5.3 | 3.30 | | 1.45 | | survived |
| | 3 | 9.0 | 114 | 391 | 4.3 | 3.30 | | 1.00 | | died |
| | Mean | | | | 4.8 | 3.30 | | 1.20 | | |
| Portal Dogs | 4 | 11.5 | 126 | 628 | 5.5 | 3.35 | | 1.25 | | survived |
| | 5 | 6.5 | 124 | 374 | 5.8 | 1.15 | | 1.30 | | survived |
| | 6 | 12.0 | 142 | 560 | 4.7 | 3.20 | | 1.10 | | died |
| | Mean | | | | 5.3 | 3.43 | | 1.22 | | |

Fig 2. Changes of arterial pressure in experimental animals reported in the present paper (WIGGERS-WERLE's method)



minutes to 4 hours and a quarter, and that of drastic hypotension was 1 hour and 10 minutes to 1 hour and a half ; one out of three cases developed irreversible shock. In both groups, animals showed a similar course and about the same mortality rate. The amount of bleeding was 4.3 to 5.3% of body weight in normal dogs (4.8% on the average), and 4.7 to 5.8% (5.3% on the average) in portal dogs, nearly the same as the former.

4) LAMSON's method

Hemorrhagic shock was induced in portal dogs by LAMSON's method and investigation was made on arterial pressure (occurrence of irreversible shock), amount of bleeding, value of hematocrit and histological findings of the liver comparing the results with those of normal dogs.

A : Course of shock

a) Method : Mongrel, adult dogs weighing from 6 to 14 kg were used. Intravenous injection of pentobarbital sodium of 25 mg/kg of body weight was given to obtain general anesthesia and 5mg/kg of heparin was also injected intravenously to prevent coagulation. The femoral arteries were exposed on both sides. As shown in Fig. 3, a glass tube of about 4 mm caliber was inserted into one of the arteries, and was connected to an irrigator with a rubber tube. The position of the irrigator was adjusted so that the blood level in the bottle was always 68 cm higher than that of the animal's heart, and thus 50 mmHg of arterial blood pressure was constantly obtained. During the experiment the amount of blood in the bottle was variable every minute and named the bleeding volume. The other artery was used for measurement of hematocrit. Fig. 4 shows a pattern of the relationship between bleeding volume and blood pressure schematically. The blood continuously ran into the bottle in the first 30 minutes to 2 hours after the start of bleeding, and then, bleeding stopped and the amount of the blood in the bottle becomes invariable for a while. As the compensatory mechanism of the circulatory system was disturbed, the blood in the bleeding bottle gradually moved back to the animal and

Fig. 3. Setting of LAMSON's method

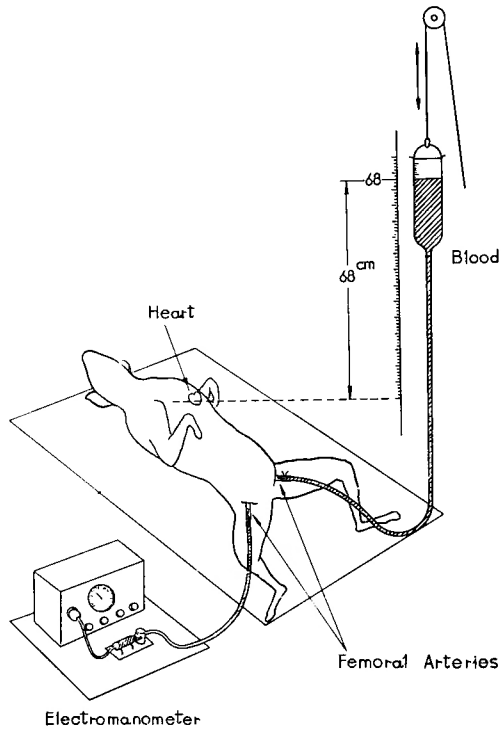
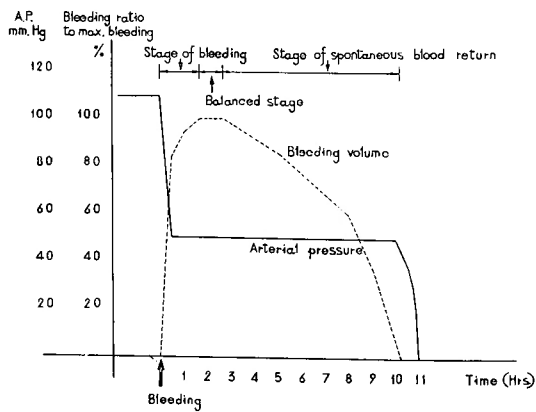


Fig. 4. Relationship between bleeding volume and arterial pressure (LAMSON's method)

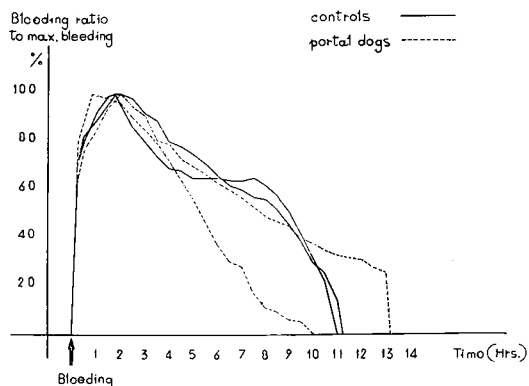


the death took place 10 to 30 minutes after the blood had returned entirely.

b) Results : Each of two normal and portal dogs were used and the results of the experiment is shown in Table 2. All died 11 to 14 hours after the time when bleeding started, and there was no practical difference between portal dogs and normal ones, but the maximum bleeding volume was 4.4 and 5.4% of body weight respectively in the former, and 4.9 and 3.8% in the latter. Fig. 5 shows the changes of bleeding volume

Table 2 Hemorrhagic Shock by LAMSON's Method

| | No. | Body Weight kg | Arterial Pressure mmHg | Maximum Bleeding | | | Period of Spontaneous Blood Return from the Time of Bleeding | | | | | Survival Period |
|-------------|-----|-------------------|---------------------------|-------------------------------------|-----------|------------------------|--|------------|------------|------------|------------|-----------------|
| | | | | Time to Max. Bleeding Hrs. Mins. | Volume cc | Ratio to Body Wt. % | 5% | 30% | 40% | 70% | 100% | |
| | | | | | | | Hrs. Mins. | Hrs. Mins. | Hrs. Mins. | Hrs. Mins. | Hrs. Mins. | |
| Controls | 7 | 6.7 | 118 | 1.45 | 325 | 4.9 | 2.45 | 5.35 | 7.00 | 10.00 | 11.15 | 11.40 |
| | 8 | 7.5 | 104 | 1.45 | 285 | 3.8 | 2.00 | 3.50 | 8.10 | 10.00 | 11.00 | 11.05 |
| Portal Dogs | 12 | 8.0 | 122 | 0.50 | 350 | 1.4 | 2.05 | 4.07 | 4.40 | 6.30 | 10.00 | 10.30 |
| | 13 | 14.0 | 110 | 2.00 | 750 | 5.4 | 2.30 | 5.00 | 6.30 | 12.15 | 13.10 | 13.43 |

Fig. 5. Changes of bleeding volume following the lapse of time (LAMSON's method)

with the lapse of time which was expressed in the term of percentage of bleeding volume to the maximum bleeding volume.

B : Development of irreversible shock

According to SUDO's²⁴⁾ experiment, even in the stage of spontaneous blood return, if returning of remaining entire blood was rapidly carried out before the spontaneous blood return of 15%, normal dogs regained normal blood pressure and no hypotension was seen more than 3 or 4 hours following the blood return ; but if blood return was made after the spontaneous blood return of 30%, marked hypotension developed within 1 to 2 hours and all dogs died in about 3 hours. In other words, dogs were in a state of reversible shock up to the stage of 15% spontaneous blood return, but at the stage of 30% spontaneous blood return, they were all in a state of irreversible shock. In the present experiment, this bleeding experiment was reproduced on five portal dogs and three normal dogs.

As shown in Table 3, the interval of time between bleeding and 30% spontaneous blood return was 5 to 11 hours and 40 minutes in normal dogs, and 4 hours and 45 minutes to 10 hours and 45 minutes in portal dogs—no significant difference between normal dogs and portal ones. But all three normal dogs died about 10 hours after blood return, while only two portal dogs died and the remaining three survived. The maximum

Table 3 Cases with Arterial Infusion at 30% Spontaneous Blood Return

| | No. | Body Weight kg | Arterial Pressure mmHg | Maximum Bleeding | | | Period of Spontaneous Blood Return | | Results |
|-------------|-----|-------------------|---------------------------|-------------------------------------|--------------|------------------------|------------------------------------|-------|----------|
| | | | | Time to Max. Bleeding Hrs. Mins. | Volume cc | Ratio to Body Wt. % | 5% | 30% | |
| Controls | 9 | 8.0 | 110 | 1.30 | 306 | 4.3 | 2.10 | 8.00 | died |
| | 10 | 6.0 | 100 | 5.30 | 314 | 5.2 | 6.40 | 11.40 | died |
| | 11 | 6.2 | 118 | 2.00 | 270 | 4.4 | 2.20 | 5.00 | died |
| Portal Dogs | 14 | 10.0 | 120 | 1.22 | 442 | 4.4 | 1.50 | 5.00 | survived |
| | 15 | 9.5 | 124 | 3.00 | 492 | 5.2 | 6.30 | 10.45 | died |
| | 16 | 8.3 | 106 | 1.15 | 382 | 4.6 | 1.45 | 4.45 | survived |
| | 17 | 7.7 | 130 | 2.10 | 420 | 5.5 | 3.20 | 8.10 | survived |
| | 18 | 7.5 | 126 | 2.00 | 362 | 4.8 | 3.20 | 9.30 | died |

bleeding volume was 3.8 to 5.2% (4.5% on the average) of body weight in five normal dogs (including the cases in which the entire course was closely observed) and 4.4 to 5.5% (4.9% on the average) of body weight in seven portal dogs. As the same could be said in WIGGERS-WERLE's method, almost equal amount of bleeding was necessitated in portal dogs in LAMSON's method (Table 4).

Table 4 Bleeding Volume in Hemorrhagic Shock

| | No. | WIGGERS-WERLE's Method | No. | LAMSON's Method |
|-------------|------|---------------------------|------|---------------------------|
| | | Ratio to Body Weight % | | Ratio to Body Weight % |
| Controls | 1 | 4.8 | 7 | 4.9 |
| | 2 | 5.3 | 8 | 3.8 |
| | 3 | 4.3 | 9 | 1.3 |
| | | | 10 | 5.2 |
| | | | 11 | 1.4 |
| | Mean | 4.8 | Mean | 4.5 |
| Portal Dogs | 4 | 5.5 | 12 | 1.4 |
| | 5 | 5.8 | 13 | 5.4 |
| | 6 | 4.7 | 14 | 4.4 |
| | | | 15 | 5.2 |
| | | | 16 | 4.6 |
| | | | 17 | 5.5 |
| | | | 18 | 4.8 |
| | Mean | 5.3 | Mean | 4.9 |

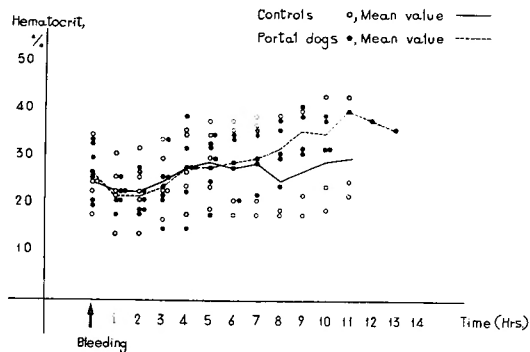
C : Variation of hematocrit

MOON²⁵⁾ emphasized the importance of increased permeability of peripheral capillaries in many types of shock and pointed out the close relationship between the concentration of circulating blood and development of shock. In the present experiment, the value of hematocrit was determined in various stages of hemorrhagic shock on both normal and portal dogs.

a) Method : Just before the bleeding, and every hour after that, blood was drawn from the femoral artery and 3 mg of potassium oxalate per 1 cc of blood was added as an anticoagulant. WINTROBE tubes were used for centrifugation at 3,000r. p. m. for 30 minutes.

b) Results : The value of hematocrit before the bleeding was 18 to 35% in normal dogs (25% on the average), while 20 to 34% in portal dogs (27% on the average). Its changes during the shock stage did not show any significant difference between normal and portal dogs. From the start of bleeding to the balanced stage, which came 1 to 3 hours later, the value of hematocrit decreased and became the lowest in the balanced stage. Then it gradually increased in the stage of spontaneous blood return, and in most cases recovered to the level before hemorrhage at the period of 20% spontaneous blood return and still continued to increase thereafter (Fig. 6).

Fig. 6. Changes of the value of hematocrit (LAMSON'S method)



D : Histological changes of liver

It is a well known fact that marked histological change appears in the liver at various types of shock. The following experiment was made, in portal dog to detect the change of liver tissue following the lapse of time in hemorrhagic shock.

a) Method : Before the bleeding, the abdominal cavity was opened through an upper median incision, and a piece of tissue of about a size of 1×1 cm was obtained from the edge of left lobe of the liver. The wound surface was managed by ligature for hemostasis. Then, withdrawal of the blood was started, coursing through the bleeding stage, the balanced stage and the stage of spontaneous blood return. A piece of liver tissue was obtained in the similar manner, as stated in the above at the time when 5%, 30% and 70% of maximum bleeding volume was spontaneously returned respectively. Specimens were stained with hematoxylin-eosin solution.

b) Results : The entire course of the bleeding is shown in Fig. 7 and Table 5. The maximum bleeding volume was 4.2% of body weight in portal dog and 4.0% in normal dog. They were both smaller than the average value of the previous experiment (1.9% and 4.5%); the length of survival time starting from the beginning of hemorrhage was 7 hours and 50 minutes, and 7 hours and 10 minutes respectively, being much shorter than that of previous experiment in which it was about 11 hours. This result

Fig. 7. Changes of bleeding volume (LAMSON's method)
Cases with histological observation of liver

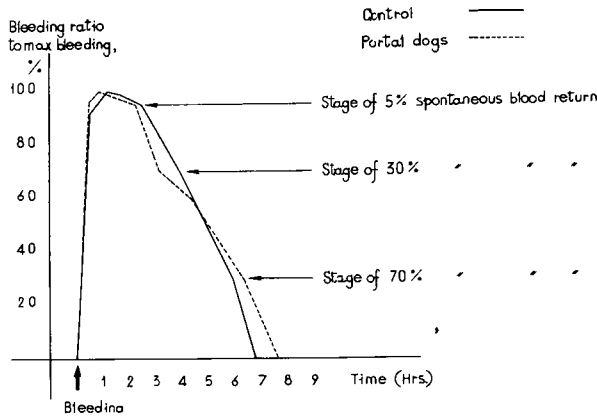


Table 5 Cases with Histological Observation of Liver
(LAMSON's Method)

| | No. | Body Weight kg | Arterial Pressure mmHg | Maximum Bleeding | | | Period of Spontaneous Blood Return from the Time of Bleeding | | | | | Survival Period |
|---------------|-----|-------------------|---------------------------|---|--------------|---------------------------|---|------------|------------|------------|------------|--------------------|
| | | | | Time to Max. Bleeding Hrs. Mins. | Volume cc | Ratio to Body Wt. % | 5% | 30% | 40% | 70% | 100% | |
| | | | | | | | Hrs. Mins. | Hrs. Mins. | Hrs. Mins. | Hrs. Mins. | Hrs. Mins. | |
| Control | 19 | 6.0 | 126 | 1.10 | 238 | 4.0 | 2.30 | 3.55 | 4.22 | 5.55 | 6.50 | 7.10 |
| Portal Dog | 20 | 12.0 | 142 | 0.50 | 504 | 4.2 | 2.10 | 3.10 | 4.20 | 6.20 | 7.40 | 7.50 |

may be interpreted to be due to the operative aggression such as laparotomy or liver biopsy.

There was no marked change in the liver of portal dog macroscopically besides slight atrophy of the lobus caudatus and quadratus. The histological findings (hematoxylin-eosin staining) were as follows :

There was no marked change in pre-hemorrhagic liver tissue besides mild hyperemia of intrahepatic vascular system and mild swelling of liver cells in portal dog (Photo. 1 & 2).

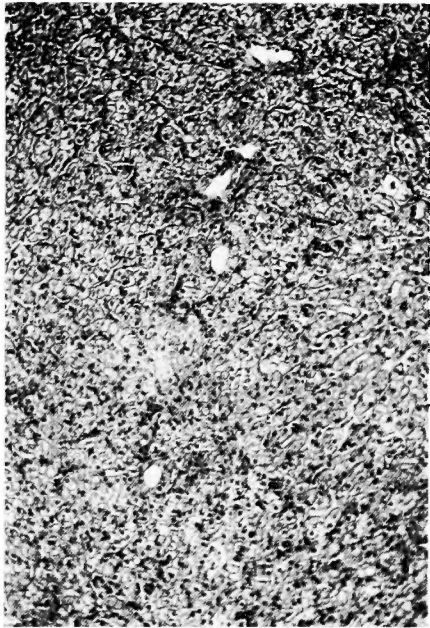
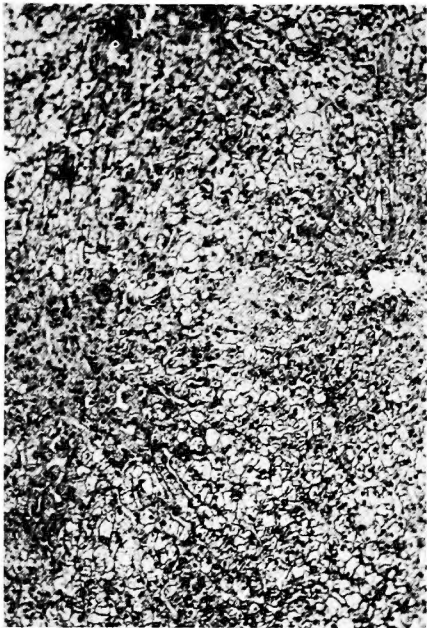
The stage of 5% blood return : In normal dog, there was the picture of standstill of polynucleated leucocytes around the central vein and GLISSON's sheath, decrease in basophilism of protoplasm of liver cells around the central vein and peripheral portion of lobulus which caused acidophilic stain and turbidity of liver cells with the decrease in liver glycogen (Photo. 3). These changes were striking in portal dog than in normal dog : vascular filling of GLISSON's sheath, central veins and sinusoids was somewhat increased, and widened lymph vessels were partly observed. Acidophilism was extended over the whole lobulus, and though partly, atrophy of cell cords appeared in the central portion of lobulus (Photo. 4).

The stage of 30% blood return : Infiltration of leucocytes, acidophilism and turbidity of liver cells became more marked in this stage. Filling of vessels was observed definitely

Histologic Pictures Stained with Hematoxylin-Eosin
before Bleeding

Control

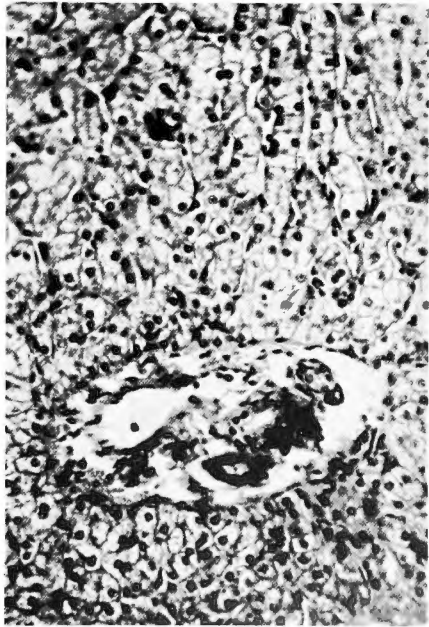
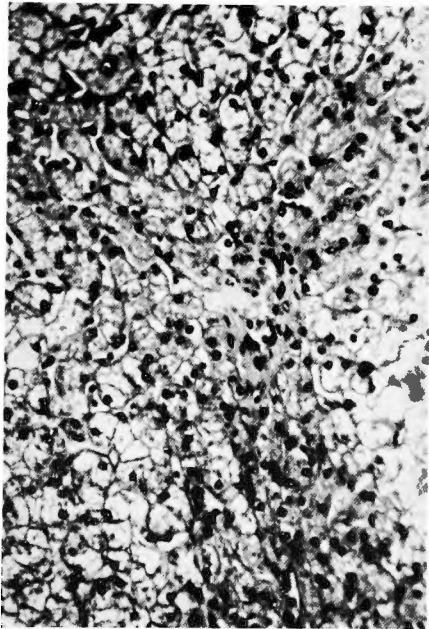
Portal Dng



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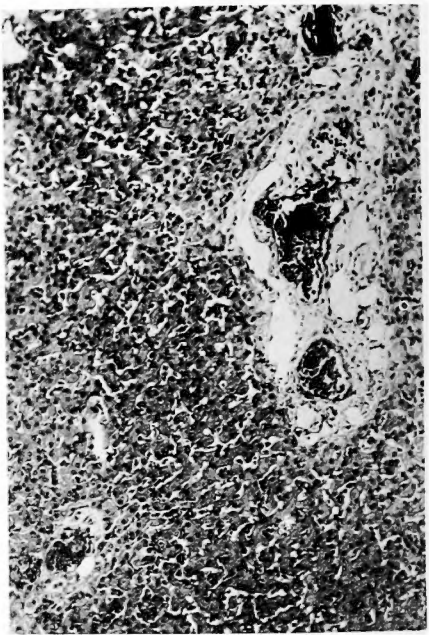
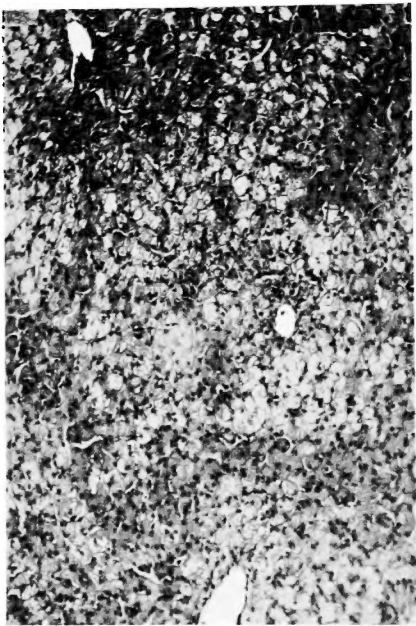


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At the Stage of 5% Spontaneous Return

Control

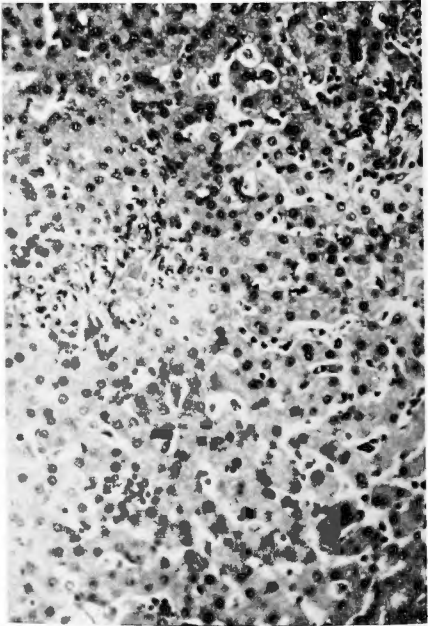
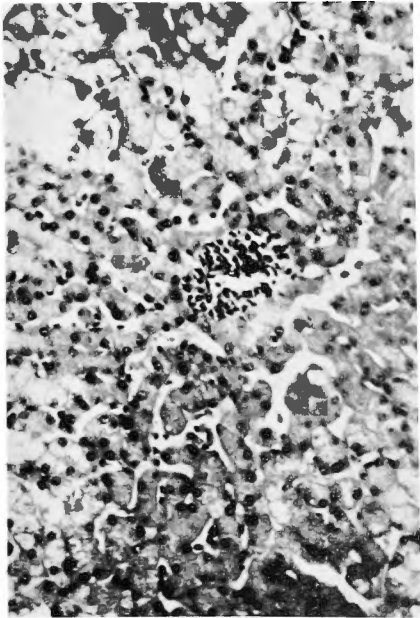
Portal Dog



(× 80)

(3)

(4)

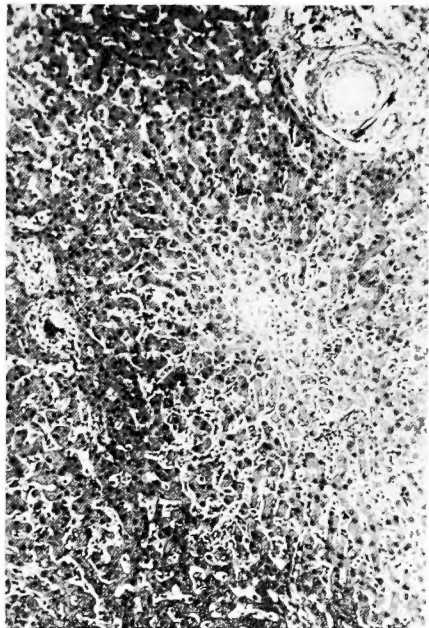
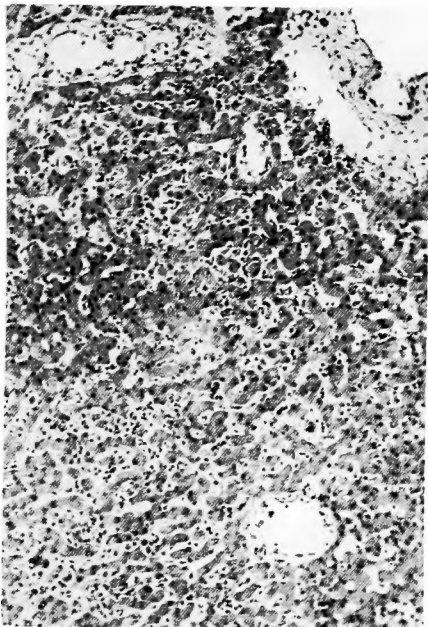


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At the Stage of 30% Spontaneous Return

Control

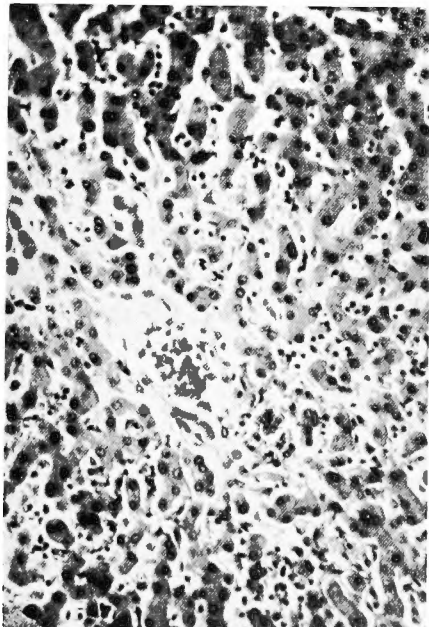
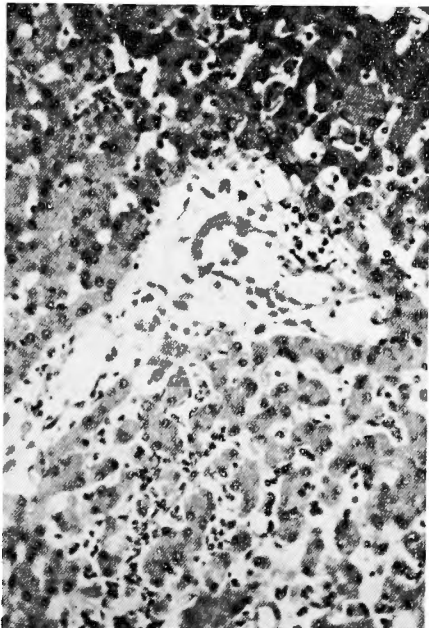
Portal Dog



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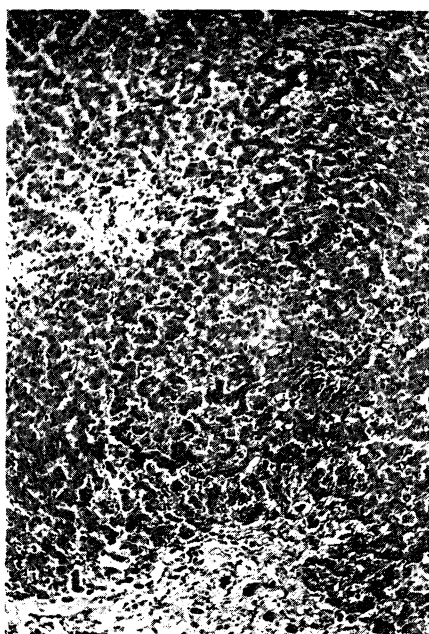
At the Stage of 70% Spontaneous Return

Control

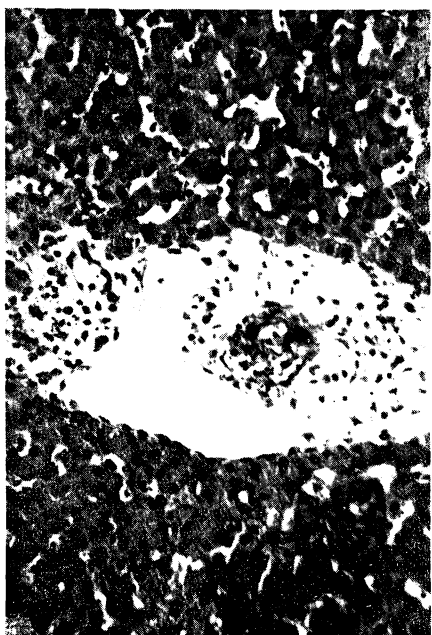


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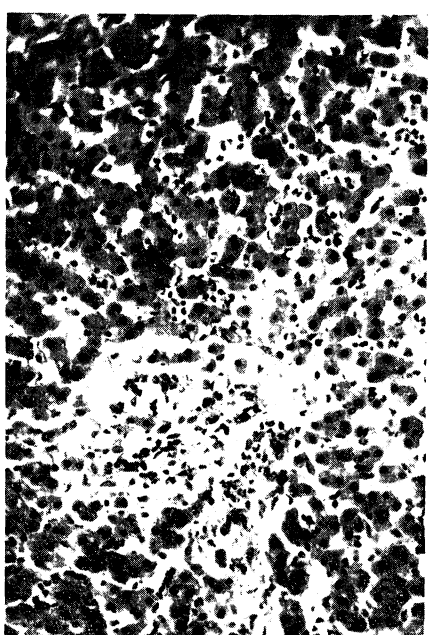
Portal Dog



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(9) (100)



(10) (100)

and connective tissue around central veins and GLISSON's sheath appeared to be edematous. Cell atrophy and vacuoles formation were noted in central portion. (Photo. 5) In portal dog, similar findings, as seen in normal one, were also noted but the picture of vascular filling was more striking, and hemorrhage was distinctly seen around GLISSON's sheath (Photo. 6).

The stage of 70% blood return : In this stage, nearly the same degree of change was seen both in portal and normal dog. With marked edema around GLISSON's sheath, intense hemorrhage was seen around blood vessels, and infiltration of polynucleated leucocytes became pronounced in sinusoids. Cell atrophy and vacuoles formation in central portion became distinct and pycnosis or even nuclear disintegration was noted in some part of lobules (Photo. 7 & 8).

Considering the above findings from the point of view of circulatory disturbances or parenchymal damages, in the early stage when spontaneous blood return started, i. e. the stage of 5 to 30% blood return, the circulatory disturbances appeared earlier and more intensely in portal dog than in normal one. The parenchymal damages also appeared somewhat greater in portal dog, although there was not so large difference as seen in circulatory disturbances. In 70% spontaneous blood return stage, when irreversible shock was definitely established, both circulatory disturbances and parenchymal damages appeared to the same degree in both portal and normal dog (Table 6).

Table 6 Histological Changes of Liver in Hemorrhagic Shock by LAMSON's Method

| | | Before Bleeding | | At the stage of 5% Spontaneous Return | | At the stage of 30% Spontaneous Return | | At the stage of 70% Spontaneous Return | |
|-------------------------|--|-----------------|------------|---------------------------------------|------------|--|------------|--|------------|
| | | Control | Portal Dog | Control | Portal Dog | Control | Portal Dog | Control | Portal Dog |
| Circulatory Disturbance | Vascular Congestion of Glisson's Capsule | — | + | — | + | + | + | + | + |
| | V. C. of Central Vein | — | + | — | + | + | + | + | + |
| | V. C. of Sinusoid | — | ± | — | ± | + | ± | ± | ± |
| | Interstitial Swelling | — | — | — | — | ± | + | + | ± |
| | Bleeding | — | — | — | — | — | + | + | + |
| | Leucocyte Infiltration | — | — | + | + | + | + | ± | ± |
| Parenchymal Damage | Eosinophilic Cytoplasm in Staining | — | — | + | ± | ± | ± | ± | ± |
| | Central Atrophy | — | — | — | ± | + | + | ± | ± |
| | Vacuolation | — | — | — | — | + | + | ± | ± |
| | Pycnosis and Karyolysis | — | — | — | — | — | — | + | + |

5) Tolerance of portal dogs against portal vein ligation

Since ORS' report, there have been many who reported that animals died in a short period of time after the ligation of the portal vein. No theory was accepted generally regarding the cause of death, but the depletion of the effective circulating blood volume into the splanchnic bed, or acute liver failure was assumed to be the probable cause. The author made the portal vein ligation on each of four portal and normal dogs and

studied the fluctuation of the arterial and the portal blood pressures.

a) Method : Mongrel, adult dogs weighing 7 to 11 kg were used as experimental animals. Under general anesthesia with intravenous injection of pentobarbital sodium of 25 mg/kg, an upper midline incision was made to expose the main branch of portal vessel. The bifurcation of splenic vein was identified. The portal vein was ligated at the liver side of this bifurcation. The portal blood pressure was monitored through a polyethylene tube, 1 mm in caliber, which was inserted into the portal vein from the distal portion of superior mesenteric vein, setting the tip of the tube near the point of portal vein ligation. The other end of the tube was connected to an erected glass tube which contained water. The arterial blood pressure was measured by a mercury manometer, which was connected to a vinyl tube inserted into the femoral artery.

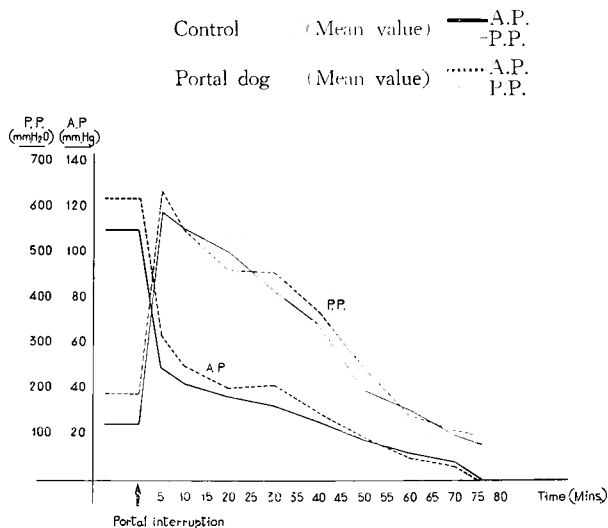
b) Results : The interval of time from the portal vein ligation to the animal's death has been reported to be 66 minutes by ELMANN & COLE, and 70 minutes by SHIMIZU.²⁶⁾ In the present experiment, as shown in Table 7, it was 45 to 78 minutes in normal dogs

Table 7 Portal Vein Interruption

| | No. | Body Weight kg | Arterial Pressure mmHg | Portal Pressure mmH ₂ O | Survival Period Min. |
|----------------|------|-------------------|---------------------------|---------------------------------------|-------------------------|
| Controls | 21 | 10.0 | 105 | 120 | 45 |
| | 22 | 7.0 | 100 | 135 | 78 |
| | 23 | 8.5 | 104 | 115 | 46 |
| | 24 | 8.3 | 135 | 140 | 74 |
| | Mean | | 111 | 128 | 61 |
| Portal Dogs | 25 | 9.2 | 120 | 240 | 78 |
| | 26 | 10.8 | 145 | 195 | 71 |
| | 27 | 9.0 | 105 | 185 | 44 |
| | 28 | 10.5 | 130 | 150 | 50 |
| | Mean | | 125 | 193 | 63 |

(61 minutes on the average) and 44 to 78 minutes in portal dogs (63 minutes on the average) revealing no significant difference. Following the lapse of time after the ligation of the portal vein, the changes of arterial blood pressure showed a similar pattern in both normal and portal dogs. The standstill of blood flow due to the portal vein ligation induced marked stagnation of blood in the viscera, and produced rapid decrease in circulating blood volume. Therefore, as shown in Fig. 8, as soon as the portal vein was ligated, the arterial blood pressure fell rapidly and became 50 mmHg in 5 to 10 minutes, then gradually came down to 10 mmHg. After that, rapid fall was noted shortly before the death, showing 0 mmHg.

The portal pressure was estimated to be from 112 to 140 mmH₂O, showing an average of 128 mmH₂O, in normal dogs before the ligation while 150 to 240 mmH₂O, 193 mmH₂O on the average, in portal dogs. According to TSUCHIYA²⁷⁾, portal pressure more than 180 mmH₂O should be regarded as portal hypertension. Therefore, it may be said that 3 of 4 portal dogs in the present experiment were in a state of portal hypertension. As for the changes of the portal pressure after the ligation of the portal vein,

Fig. 8. Changes of arterial and portal pressures after portal interruption

there was also no significant difference between portal and normal dogs. With marked visceral blood stagnation due to portal block, the portal pressure elevated rapidly and reached maximum in 3 to 5 minutes (530 to 710, 595 mmH₂O on the average for normal dogs, and 550 to 790, 640 mmH₂O on the average for portal dogs). After that, with the appearance of extensive hemorrhage in the intestine and mesenterium, the portal pressure began to fall gradually with little fluctuation showing an almost straight line, and returned close to the pre-ligation at the time of death.

DISCUSSION

Along with the development of liver surgery, there have been many discussions on pathophysiology of hepatic artery ligation. It has been said that anaerobic bacteria propagate in the liver, and all of the animals die from ensuing massive hepatic necrosis when hepatic arterial blood flow is interrupted abruptly in dogs. MARKOWITZ²³⁾ administered penicillin on these animals and lowered the mortality rate from 100 % to 35 % and assumed this effect of penicillin to be attributable to the inhibition of growth of bacteria in the liver. NAKASE⁵⁾ pointed out the fact that a marked decrease in ferritin in the liver together with its increase in the blood (the latter was evaluated indirectly from the determination of A. D. S. in the blood stream) ensued following the hepatic artery ligation, and noticed that this change must have played an important role in the development of hepatic necrosis. From this point of view, he could prevent the development of fatal liver necrosis by the use of atropin or dibenamine which restricts the mobilization of liver ferritin into the blood stream or counteracts the action of ferritin. ISHIGURO¹⁴⁾ made a histological study on the mechanism of the development of hepatic necrosis, and made it clear that the decisive factor for this necrosis is not simple anoxia due to the interruption of arterial inflow, but a secondary anoxia due to the circulatory disturbance in the hepatic venous and the portal systems, i. e, marked blood stagnation in these systems. Also,

from the fact that anaerobic bacteria were found not before but after the formation of hepatic necrosis, he assumed this growth of bacteria was nothing but an accessory phenomenon following the development of anoxic hepatic necrosis. FRASER¹⁵⁾, KURAMOTO¹⁶⁾ and MIYAZAKI¹⁷⁾ observed an absence of development of collaterals at least for two weeks after the hepatic artery ligation. The liver function which was once disturbed also recovered to a nearly normal level, within 7 to 10 days after the ligation. These results show that liver cells of portal dogs which survived the hepatic artery ligation are well adapted to the hypoxic state.

A copious number of reports have been made on the interrelation between hemorrhagic shock and the liver. Although pathological changes in major organs besides the liver are not always parallel with the shock process, those of the liver correspond fairly well to it. So, it is assumed that the liver is not only the most sensitive organ to anoxia in hemorrhagic shock but an organ which may be concerned with the provocation of irreversible shock. In this regard, SHORR⁶⁾ advocated V. D. M. theory that V. D. M. (ferritin) derived from anoxic liver plays a main role in the development of irreversible shock. FINE¹⁰⁾ explained that the toxin of anaerobic bacteria which grow in anoxic liver plays the main role. Besides these theories, there are many assumptions which emphasize the role of hepatic anoxia in the development of shock (COHN, etc.²⁸⁾). On the other hand, SELKURT²⁹⁾ and LILLEHEI³⁰⁾ considered that the liver does not enhance the development of the irreversible phase, but has a preventing effect, and they sought the cause of irreversible shock in hemorrhagic necrosis of the intestine due to circulatory disturbance, insisting on the importance of toxic substance derived from its necrotized area.

Concerning the preventive methods of irreversible shock, there are also many reports. By administering antibiotics, FINE and his associates could increase the rate of recovery in their standard type of shock-producing experiments. On the other hand, HARDY³¹⁾ and ZWEIFACH, based on their results of the same experiment as FINE's, denied the effectiveness of antibiotics, and LILLEHEI also, evaluating the results of his endotoxin shock experiment, insisted on the ineffectiveness of antibiotics. Some reported that hypothermia is effective but others³²⁾ disapproved of this. LILLEHEI³⁰⁾, AZISAWA³³⁾ and SUDO²⁴⁾ recognized the effectiveness of an autonomic nerve blocking agent, such as chlorpromazine or dibenzyline. This fact attracts our interest, when considered in reference to SHORR's V. D. M. theory. Under the administration of chlorpromazine which suppresses the activity of metabolism, the liver and other major organs acquire an insensitivity to anoxia, and at the same time this drug keeps the vascular stability with its autonomic nerve blocking action. Besides blocking the sympathetic hyperactivity, dibenzyline inhibits the SH enzyme activity and seems to have some relationship with the metabolism of ferritin which becomes vascular-active when combined with SH radical. Therefore, it is assumed that this drug has an antishock action by inhibiting the production of ferritin or by inactivating ferritin in the blood flow.

In the present experiment by WIGGERS-WERLE's method, a certain degree of hypotension was obtained, retaining for the same period of time, without any difference in mortality rate between portal and normal dogs. And the amount of bleeding which was necessary to bring forth a certain degree of hypotension in portal dogs was nearly the

same as that in normal dogs. In LAMSON's method also, almost equal was the amount of bleeding necessary to reach the balanced stage in both groups. But when the remaining entire blood was returned at the stage of 30% spontaneous blood return, irreversible shock and death occurred in all cases of normal dogs, while in portal dogs, only 2 out of 5 died of irreversible shock and the other 3 recovered from shock and survived over 48 hours.

From the above results, it was ascertained that the liver of portal dogs which had the intrahepatic circulatory disturbances immediately after the hepatic artery ligation acquires, at least, the same degree of adaptability to anoxia as that of normal ones.

As the histological changes of the liver at the time of shock, vascular filling, especially that of the central veins and their surroundings, central necrosis, appearance of watery-vacuolation, cell infiltration, destruction of the liver structure, and change of mitochondria are deemed to be principal findings. Since MOON's³¹⁾ report, there have been many who considered that the development of central necrosis is due to anoxia. There are also many who noticed at the time of shock marked decrease in liver blood flow and reduction of oxygen saturation. There is a great similarity between the mechanism of development of hepatic necrosis after hepatic artery ligation and that of hepatic necrosis in hemorrhagic shock, especially when it progresses to irreversible shock.

There was no essential difference in histological findings of the liver between those before and after the stage of 30% blood return of the maximum bleeding volume, when the shock was regarded as being progressing to irreversible one, i. e., at the stage of 15 to 20% and that of 40% spontaneous blood return. If the entire blood return was made in each stage, the progress of pathological changes was arrested in the former, while it was aggravated in the latter. From the fact that the respiration coefficient QO_2 of liver tissue falls rapidly at the stage of 30% spontaneous blood return, it is probable that in this stage, some severe disturbance in physiological function of the liver, which can not be detected by histological examination, may have taken place.

The histological study of portal dog in the present experiment revealed mild vascular filling in the blood vessel of the liver already before the bleeding was started and this change became more pronounced after the bleeding in comparison with that of normal dog. However, no essential difference was noted in the parenchymal cells of either. In other words, there was no histological finding which suggests some change in tolerance against bleeding shock in portal dog.

As for the cause of death following the sudden blockage of portal vein, many explanations have been delivered---such as intoxication theory, neurogenic theory, or hemorrhagic shock theory. However, in the present experiment, no difference in survival period after the portal ligation was noted between portal and normal dogs. Therefore, it is assumed that regarding the cause of death in shock, as ELMAN et al. have mentioned, the liver itself does not participate so much in it, but the circulatory disturbance of portal system areas seems to play an predominant role.

CONCLUSION

For the study concerning pathophysiology of the liver following hepatic artery ligation

tion, shocks by hemorrhage, and by portal vein ligation were produced on portal dogs which survived the hepatic artery interruption by the administration of penicillin. The following results were obtained :

1) No difference was noted in the rate of development of irreversible shock between portal and normal dogs in the hemorrhagic shock by WIGGERS-WERLE's method. And the amount of bleeding which is necessitated to bring forth the irreversible shock was 5.3% of body weight in portal dogs, and 4.8% in normal dogs.

2) In hemorrhagic shock by LAMSON's method, the necessitated amount of bleeding was 4.9% of body weight in portal dogs and 4.5% in normal ones.

3) In LAMSON's method, the survival period after the bleeding revealed no difference between portal and normal dogs. When artificial rapid blood return was made at the stage of 30% spontaneous blood return with the object of causing normovolemic shock, in all the normal dogs irreversible shock developed and the animals died, while only 2 out of 5 portal dogs developed the shock and the three other dogs survived over 48 hours.

4) The changes of hematocrit in portal dogs during the hemorrhagic shock followed almost the same course as those of normal ones.

5) The histological findings of the liver at each stage of hemorrhagic shock suggested somewhat higher degree of circulatory disturbance in portal dog than in normal one, but in changes of the parenchyma, no clear-cut difference was noted between the two groups.

6) The fluctuation of arterial and portal blood pressure following portal blood flow interruption and the survival period of animals showed no significant difference between portal and normal dogs.

From the above results, portal dogs which survived the hepatic artery ligation had no less tolerance against hemorrhagic shock than normal dogs.

In concluding my report, I wish to express my deepest gratitude to Dr. CHISATO ARAKI, professor of Kyoto University and Dr. ICHIO HONJO, professor of Kanazawa University for their kind and continuous guidance, encouragement and supervision.

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和 文 抄 録

門 脈 犬 の 肝 病 態 生 理

特にシ ョ ッ ク に対する抵抗性について

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Haberer が肝動脈結紮により肝動脈血流を完全に遮断すると、動物は広汎な肝壊死を起して殆んど100%死に至ることを明らかにしたが、近年Markowitz, 中瀬等によつて、肝動脈結紮後ペニシリン或はアトロピン等を投与することにより、その死亡率が約30%に迄低下することが明らかになった。このように肝動脈結紮により肝臓に流入する動脈血流を遮断し門脈血のみで致死性肝壊死を起すことなく長期生存せる犬、即ち門脈犬の肝病態生理を追究するために、門脈犬と正常犬に肝無酸素症と密接な関係をもつ出血性ショック及び門脈結紮を施して次の様な成績を得た。

実験方法；

1) 門脈犬としては総肝動脈、胃十二指腸動脈及び右胃動脈の三大動脈を二重結紮、切断し更に胆嚢を摘出した後ペニシリンを投与して生存し得た術後2週間以内の外観上健康な犬を使用した。

2) 出血性ショック作成法としては Wiggers-Werle 氏法と Lamson 氏法の2方法を試み、夫々の方法に於て不可逆ショック発生率、出血量、ヘマトクリット値の変動、肝細胞の組織学的変化を見た。

3) 門脈結紮による門脈血流遮断に際して、門脈圧及び股動脈圧の変動、死亡時間等を比較検討した。

実験成績；

1) 出血性ショックを起すために要した出血量は Wiggers-Werle 氏法で門脈犬が体重の5.3%、正常犬が1.8%であり、Lamson氏法で門脈犬が4.9%、正常犬が4.5%で、両者共門脈犬と正常犬との間に特に差違を認めなかつた。

2) 不可逆ショック発生率は Wiggers-Werle 氏法では有意の差は認められないが、Lamson 氏法では30%自然還血期で返血した場合、正常犬は従来報告の如く3例が全例不可逆ショックを起して死亡したが、門脈犬は5例中2例が不可逆ショックを起したのみで他の3例は48時間以上生存し得た。

3) 出血性ショック時のヘマトクリット値の変動は門脈犬、正常犬共に同じ経過をとり有意の差は認められなかつた。

4) 出血性ショックの各時期に於ける肝の組織学的所見では、循環障害は正常犬に比較して門脈犬にやゝ高度に発現しているが、実質障害は両者にそれほど明らかな差はみられなかつた。

5) 門脈血流遮断による動脈圧や門脈圧の変動及び生存時間等は両者に有意の差は認められなかつたが、門脈犬の4例中3例は portal hypertension であつた。

以上の成績より、出血性ショックに対する抵抗性について門脈犬は正常犬に比べて遜色なしと云える。